A randomized, open-label, phase II trial comparing neoadjuvant trastuzumab, pertuzumab and endocrine therapy +/- the PI3K inhibitor inavolisib in patients with HER2+/HR+, PIK3CA mutant early breast cancer - GeparPiPPa

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Background

PIK3CA mutations can be found in about 20%-30% of HER2-positive (+) breast cancer (BC) patients and indicate a lower response to chemotherapy and anti-HER2 therapy, especially in HER2+/hormone receptor-positive (HR+) tumours.[1,2,3] Crosstalk exists between key signaling pathways (HR, HER2 and PI3K) and inhibition of PI3K results in the activation of HER2-pathway.[4] The phase III Solar-1 study demonstrated a significant improvement in progression-free survival with the addition of alpelisib to fulvestrant in *PIK3CA* mutant metastatic BC.[5] GeparPiPPa investigates in the neoadjuvant setting the potential incremental efficacy and safety of inavolisib, an oral pure PI3Kα inhibitor, in addition to endocrine and anti-HER2 therapy in patients with early HER2+/HR+ and *PIK3CA* mutant BC.

Study Overview

GeparPiPPa (GBG 105/EUDRA-CT 2021-002323-38) is a multicenter, randomized, open-label, parallel-group, phase II study. Approximately 170 patients with early-stage HER2+/HR+, *PIK3CA* mutant BC will be randomized in a 1:1 ratio to receive neoadjuvant endocrine therapy in combination with dual anti-HER2 blockade consisting of ready-to-use fixed-dose combination of pertuzumab and trastuzumab as subcutaneous (PH-FDC SC) formulation q3w for 6 cycles (18 weeks) without or with inavolisib (9mg 1x1/d orally, day 1-21 q3w). Endocrine therapy consists of either tamoxifen 20mg or an aromatase inhibitor (1x1/d orally, day 1-21 q3w). Premenopausal women and men receive a GnRH analogue in addition to an aromatase inhibitor. After end of therapy, patients will undergo a core biopsy and/or surgery. In case of tumor residuals in the biopsy additional neoadjuvant treatment may be given. In case of ycT0 and no tumor residuals in the biopsy, it is recommended to undergo surgery. Further (neo)adjuvant systemic treatment and radiotherapy will be administered at the discretion of the investigator according to standard of care.

Objectives and Endpoint

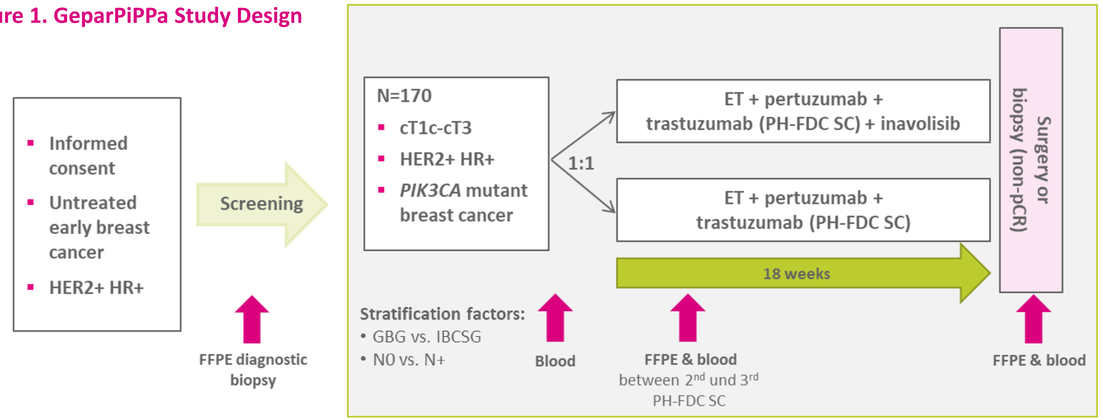
Primary objective: To compare pathological complete response (pCR=ypT0/is ypN0) rates between the two treatment arms.

Secondary objectives (selection): To assess other pCR definitions, invasive disease-free survival, overall survival, breast conservation rate, safety, tolerability and compliance.

Correlative objectives (selection, Table 1):

- To examine molecular/pathway markers on core biopsies and residual disease.
- To assess the predictive/prognostic effect of different *PIK3CA* hot spot mutations.
- Use of baseline and on-therapy specimens to explore potential new biomarkers.

Figure 1. GeparPiPPa Study Design



Study Treatment:

- Endocrine Therapy (ET): tamoxifen or an aromatase inhibitor (1x1/d orally, day 1-21 q3w) +/- gonadotropin-releasing hormone analogue
- Pertuzumab/trastuzumab as subcutaneous formulation on d1, q3w:
  - loading dose 1st cycle: 1200 mg/600 mg
  - 2nd-6th cycle: 600 mg/600 mg
- Inavolisib 9mg 1x1/d orally, day 1-21 q3w

Key Inclusion Criteria

- Age ≥ 18 years
- Females or males
- Diagnosis of a unilateral primary carcinoma of the breast by core needle biopsy
- Central testing must confirm HER2 positivity and HR positivity (according to ASCO/CAP guidelines) as well as *PIK3CA* mutation(s) (tumor)
- Primary tumor must be cT1c – cT3
- Normal cardiac function must be confirmed by ECG and cardiac ultrasound (LVEF ≥55%)
- Complete staging work-up within prior to randomization

Key Exclusion Criteria

- Excisional biopsy or lumpectomy and/or surgical axillary staging procedure prior to randomization
- Patients with definitive clinical or radiologic evidence of Stage IV BC
- Need of immediate neoadjuvant chemotherapy, e.g. inflammatory BC
- Body-Mass Index >30
- Patients with diabetes mellitus type I or uncontrolled type II
- Patients with currently documented pneumonitis/interstitial lung disease
- Patients with active uveitis or vitritis, history of uveitis, or active infectious process in the eye

Collection of Biomaterial

Study requirements	Screening	Pre-treatment	After 2nd/ before 3rd dose of PH-FDC SC	At end of treatment
FFPE tissue breast tumor (biopsy)	X		X	X
Whole Blood		X		
Plasma collection ctDNA		X	X	X

Abbreviations: ctDNA: circulating tumor DNA; FFPE: formalin-fixed, paraffin-embedded

Recruitment

- It is planned to conduct the study within approximately 50 GBG and IBCSG sites.
- First patient in Q IV/2022.

References

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Presented at: ESMO Congress 2022, 9-13 September 2022

The trial is financially supported by F. Hoffmann-La Roche Ltd

Disclosure statement: SL reported grants and honorarium from Abbvie, AstraZeneca, BMS, Gilead, Novartis, Pfizer, Roche, Daiichi-Sankyo; honorarium from Amgen, Eirgenix, GSK, Lilly, Merk, Pierre-Fabre, Seagen, Sanofi; patents pending EP14153692.0, EP21152186.9, EP19808852.8, issued EP15702464.7, Digital Ki67 Evaluator; all paid to the institute